DISCUSSION
DISCUSSION

The present study comprised of 21 children including 12 cases having cerebral malaria and 9 children who were healthy (control). Cases of cerebral malaria were selected strictly according to the criteria laid down by Warell et al (1982). All the patients were in an unarousable coma. All had asexual forms of malaria parasite in their peripheral smears. None of them had any clinical evidence of other encephalopathies.

Control cases were picked up from normal children of hospital staff, or sibs accompanying the patients seen in the O.P.D. or who were admitted in the hospital. Carefully taken history and examination of the control cases excluded any possibility of primary or secondary immunological disorder being present in them. History of any drug intake that would have affected the immune status was also sought to exclude such cases.

1. **Age distribution**

Age distribution of the patients included in the study was strikingly different from that reported in foreign literature. Eleven out of 12 cases of cerebral malaria were aged 5 years or more. One case was 1½ years old.

Hendra in et al (1970) found preponderance of cerebral complications mainly under 3 years of age, 144 out of total 171 children who had convulsions were
less than 5 years of age (84.2%) in the Nigerian population studied by them.

Osuntokun (1963), and Bruce Chwatt (1970) and Expert Committee of the W.H.O. Malaria Action Programme (1986) also reported higher incidence of cerebral malaria under 5 years of age in children residing in endemic areas, owing to lower immunity in them. But, on the other hand, Indian literature shows higher incidence of cerebral malaria above 5 years of age as shown in table - IX.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Name of worker</th>
<th>Reported age group</th>
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<tr>
<td></td>
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<td>distribution</td>
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<tr>
<td>1.</td>
<td>Ahmed et al</td>
<td>1986</td>
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<tr>
<td></td>
<td>(Aligarh)</td>
<td>0-3 Yrs. (5)</td>
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<td></td>
<td></td>
<td>4-7 Yrs. (9)</td>
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<td></td>
<td>7-8 Yrs. (16)</td>
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<td>2.</td>
<td>Sachdeva et al</td>
<td>1985</td>
</tr>
<tr>
<td></td>
<td>(Delhi)</td>
<td>4-8 Yrs. (3)</td>
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<td></td>
<td></td>
<td>8-12 Yrs. (3)</td>
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<td>3.</td>
<td>Kidwai et al</td>
<td>1986</td>
</tr>
<tr>
<td></td>
<td>(Aligarh)</td>
<td>&lt; 2 Yrs. (1)</td>
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<td></td>
<td></td>
<td>2-6 Yrs. (5)</td>
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<td>6-12 Yrs. (13)</td>
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Thus, in the present study age incidence was similar to what has been observed by other Indian workers. This finding is against the theory that relative non immunity of children below 5 years of age renders them more susceptible to complications of malaria. It could not be expected that children below 5 years of age residing in Bundelkhand region would remain nonimmune to malaria. In fact, malaria is commonly seen in all the age groups in this region including children below five years of age.
2. Sex distribution

The sex distribution of the patients included in the present study showed male preponderance (75%) (Table-II). This male preponderance was similar to what has been reported by other Indian authors. Sachdeva et al (1985) and Ahmed et al (1986) reported a male female ratio of 2:1. Kidwai et al (1986) reported a ratio of 4:1. Other Indian studies quoted by Ahmad et al vis. Gautam et al (1980) and Patwarda et al (1978) also had a male preponderance. Hendrickson et al (1971), Petuchla et al (1977), Adams et al (1981), Srikanth et al (1975) also found similar male preponderance in their series of cases.

3. Mean body weight

On the whole mean body weight of the patients included in the present study did not fall in the category of protein energy malnutrition as per the criteria laid down by the Indian Academy of Paediatrics (table-III). However, 2 individuals among the group of patients were malnourished (grade II malnutrition). Thus in all about 17% (2/12) cases were malnourished.

It has been observed by Edington (1967) and Hendrickson et al (1971) that convulsions and cerebral malaria were common in well nourished children compared to malnourished cases. Osmankam (1983) explained this observation on the basis of impaired delayed hypersensitivity and cellular immunity in PEM and associated thymic
atrophy. Relatively low incidence of cerebral malaria in malnourished children in the present study strengthens the previous observations and calls for the need to explain the pathogenesis of cerebral malaria on the basis of immunological mechanisms. Mean body weight (expressed as percentage of Harvard standards) of patients and control cases was almost similar as is evident from table-III. This helped to minimize the variation in complement levels in two groups of cases that would have occurred as a result of malnutrition.

4. Caustive agent of cerebral malaria

In the present study 4 out of 12 cases showed evidence of asexual forms of P. vivax alone in their peripheral blood smear. A thorough search made in several slides of each patient did not show any evidence of Plasmodium falciparum. Only one out of 12 cases had mixed infection of P. vivax and P. falciparum. Remaining 7 cases were caused by P. falciparum.

It is evident from the above observations that cases of cerebral malaria do occur in Plasmodium vivax infection. All the four cases reported in the present study had the clinical picture resembling classical picture of falciparum cerebral malaria (Table-III). All the four patients had fever, convulsion(s) and deep coma. The mortality rate was significantly higher than observed in falciparum malaria. Two cases died (50%), while only 1 out of 7
cases of falciparum cerebral malaria (28.5%) died. These mortality figures are similar to that observed by Sachdeva et al (1985) who reported 66% mortality in their series of vivax cerebral malaria.


Kitchen (1949) believed that such cases could be due to an unfavourable premorbid background or intercurrent infection. In the present series all the cases were normal prior to the ailment and two cases did respond to chloroquine therapy alone within 2 days of therapy. If viral encephalitis is thought to be an associated factor (Leben and Polonsk, 1983) then the present observations go against this since in viral infections an early recovery is quite unusual.
Hill et al (1963), Chabbesse et al (1981) and Leheb and Polozak (1985) also kept in the possibility of mixed infection due to *P. falciparum* infection. But a thorough search in the Giemsa stained smears in the present study, did not reveal any stage of *P. falciparum* in such cases.

5. **Haemoglobin, Total and Differential Leukocyte Counts and E.S.R. (Table-IV)**

Mean value of haemoglobin was significantly low (10.7±1.76 gm%) in the patients of cerebral malaria than in the control group (12.7±0.69 gm%) i.e. *P < 0.005.*

This findings was similar to the finding of Malaria Action Programme Expert Committee (1986).

However, no significant difference was observed when comparison was made between the cases of *falciparum* (10.06±1.98 gm%) and *vivax* cerebral malaria (11.3±5.2 gm%).

Values of haemoglobin were in the range of severe anaemia (7.2 and 7.4 gm%) in two patients of *falciparum* cerebral malaria according to the criteria laid by the *WHO* (1986) i.e. haemoglobin level < 7.1 gm/dl.

Higher degree of anaemia in *falciparum* malaria is explained by heavy parasitemia observed in such cases. *P. falciparum* attacks both early and late forms of RBC's (Chatterjee, 1980). Autoimmune mechanism has been proposed by Rosenberg et al (1973) and Stanley et al (1984). But Greenwood et al (1978) attributed the haemolytic anaemia, observed in *P. falciparum* malaria, to a higher
degree of invasion of RBC's by the parasite. They could not find any significant autoimmune mechanism operating to explain haemolytic anaemia.

Total leukocyte count in patients of cerebral malaria showed mean value within the normal range (4000-11,000/mm$^3$) and was not significantly different from the control group. Differential counts were also in the normal range ($\%$ 50-75, L25-50, B0-4, M 0-8). This was similar to what observed by Schwatz et al (1950), Fisher et al (1970), Reiley and Barret (1971).

E.S.R. was significantly raised in patients of cerebral malaria (38.8±10.44 mm). It was also in conformity with the previous findings (Leban and Polesak, 1985).

**Duration of fever, haemoglobin level, icterus and outcome (Table-Y)**

Haemoglobin level was low where the duration of fever was prolonged.

No definite pattern was observed between the duration of fever and outcome of illness.

One patient of jaundice died while the other survived.

Vivax cerebral malaria showed higher mortality (50%). One patient who had mixed infection also died. Mortality figure in falciparum malaria was 39.3%.
**Clinical features**

As is evident from table VI, fever was present in all the cases of cerebral malaria. One patient had fever 15 days prior to hospitalization for which she received chloroquine and responded to it. She was comatose but did not have fever at the time of admission. However she developed it after one day after hospitalization. The same patient had mixed infection of *P. falciparum* and *P. vivax*. This observation is against the fact that in children fever developed even than relatively mild infection (W.H.O. 1986). On the other hand, expert committee of W.H.O. Malaria Action Programme (1986) states that occasionally the temperature is normal or even subnormal in severe malaria.

Classical chills and rigors were present in all the cases infected by *P. vivax*. But, three out of seven patients of falciparum malaria did not have a definite evidence of chills and rigors. This observation confirms the view of earlier workers (Bruce Chwatt, 1978, Leban & Polosak, 1985, W.H.O. 1986), that classical picture of malarial fever is generally less prominent in falciparum infection.

Headache was present in 6 out of 12 cases. The headache might have been due to malaria fever itself and not necessarily due to increased intracranial tension. Rise of intracranial tension is not prominent in cerebral malaria (W.H.O. Malaria Action Programme, 1986).
Three patients had vomiting and two other patients had loose motions. Vomiting in these cases was not projectile and was not associated with any drug intake (chloroquine). Thus, in children vomiting could be present in malaria which is sometimes a prominent complaint (Bruce Chwatt, 1979). This observation calls for a high index of suspicion for malaria in endemic areas.

Pallor was not significant in P. vivax infection and also in the majority cases of P. falciparum infection. Two patients of cerebral malaria who had moderate to severe pallor also had icterus suggesting haemolytic nature of anaemia. In one of the patients deep icterus was not associated with any liver dysfunction as the investigations revealed. This confirms the view expressed by an Expert Committee of WHO Malaria Action Programme (1986). On the other hand this finding is contrary to reports of Ramchandran and Perera (1976) and Martella et al (1969) who found hepatic dysfunction in malaria. Copinathan et al (1982) have described a malarial hepatitis in nine patients of severe falciparum malaria on the basis of conjugated bilirubinemia and slightly raised alkaline phosphatase. In one of the patients of this series, unconjugated bilirubinemia was present and alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase were normal. Level of bilirubin was 6.0 mg/dl. The other patient with icterus could not be investigated for liver.
dysfunction since he was diagnosed as a case of cerebral malaria and responded to antimalarial therapy, promptly.

Convulsions were present in all the cases of present study (100%). This incidence is higher than what has been reported previously by Daraff et al, 1967 (10%), Gopinathan et al, 1982 (15%), Osuntokun, 1983 (50%) and Ahmad et al, 1986 (76.7%). Findings in the present study are quite close to the observations of Sachdeva et al, 1985 (83.3%). This discrepancy can be explained on the basis of strict sampling (according to criteria of Warrell et al, 1986) procedure that has been followed in the present study which made it obligatory to exclude cases of mild impairment of consciousness. It is possible that in mild cases the incidence of convulsion is less. Criteria followed by Sachdeva et al who observed a higher incidence of convulsions (83.3%), were the same as given by Warrell et al.

Convulsions were generalized in all but one case who later on was seen to have a left sided hemiparesis when examined after he had recovered his consciousness. Initially for 3-4 days this patient also had left facial paresis which improved later on. But, the paresis of upper and lower limbs persisted even 9 days after the recovery of consciousness. This, confirms the findings of Bruce Chetia (1978) that sequelae may be present in severe form of cerebral malaria. Haroon et al (1978) also described permanent sequelae in cerebral malaria.
Neuropsychiatric manifestations during the phase of recovery have been described by (Daroff et al. 1967), Gopinathan et al. (1982) and Osuntokun et al. (1983). In the present study there was one patient who had confusion delirium and abnormal behaviour 2–3 days before starting the quinine therapy. He recovered fully confirming the observations made by above mentioned authors. Haemoglobinuria was present in one patient who had deep icterus. This lends evidence for massive haemolysis in that patient who also had severe anaemia (Hb 7.2 gm%).

Spleen was palpable in all the cases. Most of the cases had palpable spleen 0.5 to 1.0 cm below the left subcostal margin. However, splenomegaly was absent in 23.3% cases described by Sachdeva et al. (1985) and 23.3% cases described by Ahmed et al. (1986). Loban and Polosak (1985) maintained the view that splenomegaly became evident earlier in the patients having previous attacks of malaria. Thus it can be inferred from observations of the present study that children included probably had malaria in the past. Indeed, past history of malaria like illness was recorded in 9 out of 13 cases. This observation is significant since it goes contrary to the theory that cerebral malaria is common in non-immune children (Bruce Chwatt, 1979 and Experiment Committee of WHO Malaria Action Programme, 1986 and Osuntokun, 1983).
Hepatomegaly was present in only 2 patients (7 1cm). Others had either less than 1 cm liver enlargement or else the liver was not palpable. Hepatomegaly is early in younger children (Bruce Chwatt 1978; W.H.O. 1986). In the present study also the only child who was less than 5 years of age (1½ years) had liver size of 3.0 cm, with just palpable spleen.

Signs of collapse and peripheral circulatory failure were present in 2 patients of cerebral malaria. Going by the criteria of Bruce Chwatt (1978), Gopinathan et al (1982), Loben and Polozak (1983), WHO Malaria Action Programme (1986) that multiple complications of malaria could be seen in single patient, picture of algid malaria (collapse) was present in two cases of this study. Indeed, they required dopamine drip besides low molecular weight dextrans for the maintenance of blood pressure.

None of the patients showed any evidence of bleeding. Bleeding and clotting disturbances were previously described as being important pathogenic mechanism in cerebral malaria (Devakul et al 1966), Jaroonsasuma, 1972, Srikanthiul et al 1975). But Philips et al (1986) found significant bleeding in only about 5% of patients of cerebral malaria. Present observation is in quite agreement with the finding of Philips et al (1986). In fact Expert Committee of W.H.O. Malaria Action Programme (1986) observed that disseminated intravascular coagulation leading to
bleeding in cerebral malaria is not an important mechanism for its pathogenesis.

8. **Serum complement**

As shown in table VII & VIII mean serum complement C3 level was significantly lower (P < 0.01) in patients of cerebral malaria as compared to normal controls.

Mean value of serum complement C4 was low in patients of cerebral malaria being 75.3% of mean values of normal controls. However, the difference was not statistically significant. Mean value of C3 in falciparum was also significantly lower than that found in P. vivax infection (P = 0.05).

Mean value of C4 in P. falciparum infection was 76% of mean of observed in P. vivax infection. But the difference was not statistically significant (P > 0.5).

Evidence of hypocomplementemia has been found in both experimental and human studies of malaria with or without associated complications. Among the experimental studies, Fogel (1966) and Cooper and Fogel (1966) found depressed levels of complement components C1, C3 and C3 in P. knowlesi infected Rhesus monkeys.

Wright (1968) and Wright et al (1971) noted depressed complement levels in hamsters with P. berghei cerebral malaria.

Hoobn and Williams (1974) noticed initial increase of C4, C3 associated with peak parasitemia followed by a
decrease of these components far below to their normal range in owl monkeys infected with \textit{P. falciparum} or \textit{P. brasilianum}. The scientific group of W.H.O. (1975) reported unpublished data of Kretti et al who found initial increase in the first 3 days of infection followed by a marked fall after fourth day in mice infected with \textit{P. berghei}.

June et al (1979) observed that serum C3 level in \textit{P. berghei} infected mice was within the normal range until 9th day of infection when sudden decrease was observed in untreated animals the level continued to fall even after the 9th day. Similar findings of depression of C3 in \textit{P. berghei} infected mice were observed by contreras et al (1983), Finley et al (1982) also noted depression of C3 in \textit{P. berghei} infected mice.

Among the human studies since the first report of depression of complement in human malaria by cathaire (1910) and Vincent (1910) there are many similar reports. Dulaney (1948) reported depression of complement in human malaria.


Rosenburg et al (1973) noted a fall of C3 in falciparum malaria with anaemia.

Greenwood and Brusten (1974) found significantly
depressed values of C3 and C4 in cerebral malaria as compared to normal controls.

Srikaishul et al (1975) found marked depression of C3 in complicated malaria. Patzelai et al (1977) also noted a fall in C3 and C4 values besides a similar depression in the values of other complement components. They found evidence of activation of alternative pathway in 2 patients in addition to the activation of classical pathway.

Williams (1978) also reported hypocomplementemia in children with falciparum malaria.


Significantly lower mean value of C3 in patients with falciparum cerebral malaria as compared to vivax cerebral malaria is in agreement with the findings of Kiduni et al (1983). However, they did not notice any significant difference between mean C3 values of two species. Similarly in the present study, C4 values in two groups of patients infected with P. falciparum and P. vivax species did not show any significant difference.
Two patients of vivax cerebral malaria had higher values of C3 than the mean value seen in healthy controls. Two other patients, one with vivax cerebral malaria and another with falciparum cerebral malaria had significantly higher mean C4 value than that seen in normal controls.

These deviations from general trend can be explained on the basis of acute phase response to infection where increased production may mask the utilization (Petchelai et al, 1977 and Phamuphek et al 1985). Similar findings have been observed by Lambert and Mumba in experimental models, where the levels of C3 and C4 increased during the peak of parasitemia followed by a fall. Jume et al (1979) also found normal values of C3 and C4 like Kratti et al, in the initial phase of infection followed by a fall, in their experimental models.

Since both C3 and C4 levels are depressed it can be reasonably inferred that activation of classical complement pathway occurred in cases of cerebral malaria in the present study.

Present observation regarding C3 values being significantly lower in P. falciparum than P. vivax group in the presence of almost equal C4 values, is difficult to explain. However, Petchelai et al (1977) and Stanley et al (1984) noted activation of alternative pathway in falciparum malaria besides classical pathway. Stanley (1984) found that surface erythrocytes infected by trophozoite stage
of \textit{P. falciparum} activated alternative pathway. Thus, 
activation of alternative pathway, resulting in increased 
consumption of C3 in falciparum malaria could presumably 
explain the present finding. No comparable report could 
be traced in the literature showing activation of alter-
native pathway in vivax malaria. On the other hand, 
Phanuphak et al (1985) and Greenwood and Bruston (1974) 
did not find any evidence of activation of alternative 
pathway in falciparum malaria.

There was no correlation between levels of C3 and C4 
in the serum and duration of coma. Similar observations 
were made by Greenwood and Bruston (1974).

There was also no correlation between the outcome of 
disease and the value of complement C3 and C4 in the serum. 
Out of the two patients, both of whom had very low levels 
of C3, one did not have any detectable level of C4 as well. 
The other patient had very low level of C4. First of 
these two patients died while the other one survived. But 
the patient who survived did not initially respond to 
chloroquin and grade I unconsciousness persisted till 
quinine therapy was started. However, in general, levels 
of C3 and C4 did not correlate with the outcome. This 
finding is in variance with Ahmed et al (1986) and Kidani 
et al (1986) who found positive correlation between 
complement values (C3 and C4) and the survival. Futshelai 
et al (1977) and Sihabata et al (1975) also found.
relation between hypocomplementemia and complications in falciparum malaria. Greenwood and Brunton (1974), Phamuphak et al (1985) and Pribourg et al (1986) did not find any correlation between the levels of complement in two groups of the patients i.e. malaria and cerebral malaria.

These authors have concluded that since there was no significant difference of complement levels between these two groups of malaria cases it could be reasonably inferred that there was no significant difference of complement levels between better prognosis and poor prognosis. However these authors did not give data of outcome in their patients of cerebral malaria.

C3 and C4 in circulating immune complexes (CIC)

Polyethylene glycol (PEG) precipitation method is a non-specific method of separation of immune complexes. Various authors like Chie et al (1977) and Jens et al (1982) have found that material precipitated by PEG at low concentrations consists of immune complexes.

In the present study 4% polyethylene glycol (PEG) was used to precipitate immune complexes. Redissolved precipitate (CIC) obtained from serum of each case was subjected to complement study.

As shown in the table-VII and VIII neither the level of C3 in circulating immune complexes nor percentage of C3 bound to circulating immune complexes was significantly raised in patients, in comparison to healthy controls.
However, mean percentage of C4 linked to circulating immune complexes was significantly higher ($P<0.01$) in patients than that in controls.

In the patients of systemic lupus erythematosus significantly higher percentage of C3 in circulating immune complexes is due to its linkage to small immune complexes (Chia et al 1977). Since there was no significant difference in the percentage C3 linked to CIC in patients and control cases, in the present study, one can assume that small complexes were not in higher amount in patients of cerebral malaria as compared to controls. On the other hand, higher percentage of C4 linked to CIC in patients than in controls points out the presence of these complexes in the sera of the patients which activate classical pathway. Complement C4 is a part of classical pathway. According to Haynes and Fauci (1987), immune complexes of Ig M-Ig G class activate classical pathway of complement system while immune complexes of Ig A class activate alternative pathway. Thus it can be said that in present study immune complexes of Ig G - Ig M class were, probably, present in a significant amount in the patients and were probably of moderate to large size. This is not a new observation. A number of workers have reported formation of immune complexes in experimental as well as human malaria with or without complication which has been associated with the pathogenesis of complications of malaria.
Formation of immune complexes, their deposition in glomerular basement membrane leading to nephrotic syndrome in Plasmodium malariae infection is proved beyond doubt (and et al., 1969, Allison et al., 1969, Idris Mohd., 1982). Certain authors like Shamarspravati et al. (1973) have also found evidence of soluble immune complexes and their deposition in glomerular basement membrane in the patients of falciparum malaria presenting with glomerulonephritis. Houba et al. (1979) also proposed immune complex mechanism in falciparum malaria presenting as glomerulonephritis.

Similarly, immune complexes have been reported by Weis (1978), Boompachnavig et al. (1979), June et al. (1979), Contreras et al. (1980), Finley et al. (1982) in mice infected by P. berghei. Ehlrich et al. (1981) noticed elevated circulating immune complexes and their subsequent deposition in kidneys of P. falciparum of P. berghei infected rats.

June et al. (1979) found evidence of deposition of immune complexes in the choroid plexus of mice infected with P. berghei and having cerebral malaria. Observations of Finley et al. (1982), were no less important. They noticed that intact immune system is necessary for the expression of cerebral malaria. In their experimental models of T. cell dependent mice and T. cell independent mice, cerebral malaria was more severe in T-cell independent mice, whereas immune system was intact. Formation of circulating immune complexes was also more in such mice.
Findings of Finley et al support the previous findings of Wright (1968) and Wright et al (1971) who found that in neonatal thymectomy or administration of antithymocyte serum—golden hamsters infected by P. berghei almost suppressed the development of acute haemorrhages of the brain due to an intravascular antigen—antibody reaction.

Thus, there is enough experimental evidence to support immune complex nature of cerebral malaria in animals. All of the above workers also noticed simultaneous hypocomplementemia with the formation of circulating immune complexes pointing out that complement activation by immune complexes may be an important pathogenic mechanism.

Similarly, among human studies, Perin et al (1979) and Srikaichul et al (1975) found evidence of circulating immune complexes associated with hypocomplementemia in falciparum malaria. Srikaichul et al (1975) proposed that disseminated intravascular coagulation and release of kinins secondary to activation of complement by immune complexes, could be considered important mechanism for complications of cerebral malaria.

Previously, Greenwood and Bruston (1974) hypothesised a mechanism quite similar to Srikaichul et al (1975). They also found evidence of immune complexes and their association with hypocomplementemia. Phanuphak et al (1986) also found immune complexes in falciparum malaria with or without complication, but like Srikaichul et al
they could not find any correlation between the level of complement and immune complexes.

Adase et al (1981) showed that circulating immune complexes were found in cerebral malaria, and that their formation was associated with the reduction in complement levels. One of the most significant finding in their study was the deepening of coma in some patients after starting quinine therapy which was associated with the release of antigens of malaria parasite and their interaction with antimalarial antibodies (Ag-Ab complex formation). Torö and Roman (1978) proposed that since cerebral malaria was a disseminated vasculomelanopathy it could result from a "hypersensitive" reaction of CNS to falciparum antigens. They proposed an immune complex vasculitis of brain vasculature.

Sachdeva et al (1985) also reported formation of circulating immune complexes in cerebral malaria.

According to Idris Mohamed (1982) immune complexes could cause cerebral malaria either by their deposition into the vasculature of brain or by causing other reactions while being in circulation itself. Though deposits of immune complexes in brain were found by June et al (1979) in their study over mice, Mophersam et al (1983) did not find any evidence of immune complex deposits in human brain, on autopsy of patients of cerebral malaria.

Whatever may be the mechanism in the formation of circulating immune complexes, their association with
hypocomplementemia does point to activation of complement system by immune complexes. Complement activation itself may cause damage like, shock and disseminated intravascular coagulation.